59. A kit for detecting the presence of a target nucleic acid in a sample, comprising:

(a) a FEN-1 polypeptide;

(b) a first polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region capable of specifically hybridizing to a first portion of a target nucleic acid of interest and a 5'-region located immediately 5' to the 3'-region; and

(c) a second polynucleotide probe comprising a 5'-region capable of specifically hybridizing to a second portion of the target nucleic acid which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the first probe and the 5'-region of the second probe are capable of specifically hybridizing immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule to form a structure that is capable of being bound or cleaved by the FEN-1 polypeptide.

REMARKS

Claims 1-73 are pending and under consideration. Claims 7, 21, 36, 51 and 59 have been amended. No claims have been added or canceled. Applicant notes with appreciation that Claims 1-6 are indicated as being allowed. The various substantive rejections of the remaining claims, as well as the other defects noted by the Examiner, are addressed in detail below in the order raised in the Office Action.

1. THE AMENDMENTS OF THE CLAIMS

Claims 7, 21, 36, 51 and 59 have been amended to clarify that the polynucleotide probe which includes the 5'-flap region is a polynucleotide capable of being cleaved by a FEN-1 polypeptide. In addition, Claim 7 has been amended to delete "or" in step (c) in favor of "and/or" to clarify that the cleavage can be either detected or quantified, or both detected and quantified. A similar amendment was made to step (b) of Claim 21.

These amendments are supported throughout the disclosure of the issued patent as originally filed, and therefore do not constitute new matter. In particular, the amendments are supported at, for example, Col. 42, line 64 through Col. 43, line 36, which teaches methods utilizing polynucleotide probes and a target nucleic acid that form a 5'-flap structure capable of being cleaved with a FEN-1 polypeptide, thereby releasing nucleotides (or polynucleotides) of the 5'-flap polynucleotide probe (see specifically Col. 42, line 63 through Col. 43, line 5). Also specifically taught is optional quantification following detection of the cleavage (see specifically

Col. 43, lines 8-12). Since the amendments do not constitute new matter, entry into the instant application is kindly requested.

2. SURRENDERING OF ORIGINAL PATENT

The Examiner alleges the instant reissue application was filed without an offer to surrender the original patent. Applicant submits that an offer to surrender the original patent is already of record– it was included with Applicant's response to the Notice to File Missing Parts of Application mailed 24 July 2000. For the convenience of the Examiner, a copy of the offer to surrender, along with a copy of the stamped postcard indicating that the offer to surrender was received by the Patent Office on September 11, 2000, is attached hereto as Exhibit C. Upon indication of allowance of this reissue application, Applicant will surrender the original patent.

3. REJECTION OF CLAIMS 7-73 UNDER 35 U.S.C. § 251 AND 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7-73 stand rejected under 35 U.S.C. § 251as being based upon new matter added to the patent for which reissue is sought. Applicant traverses the rejection.

It is well settled that replacing subject matter incorporated into an application by reference with the actual text and figures of the incorporated document does not constitute new matter. As articulated by the Manual of Patent Examining Procedure (MPEP):

> Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. * * * *Replacing the identified material incorporated by reference with the actual text is not new matter.*

MPEP 2163.07(b) (emphasis added). The actual text and figures of the incorporated Harrington & Lieber article (Harrington & Lieber, 1995, J. Biol. Chem. 270:4503-4508; hereinafter "H&L") that were explicitly added to the instant reissue application by amendment therefore do not constitute new matter.

The Examiner acknowledges these amendments are proper (see Office Action, page 3, lines 9-10), yet at the same time contends Claims 7-73 are based upon new matter. Specifically, the Examiner alleges that neither the issued patent nor the incorporated H&L article describes the method steps of Claims 7-73, and invites Applicant to point to the actual text of the incorporated

H&L article or issued patent to overcome the rejection (Office Action, page 3, lines 11-14). The rejection is traversed on the ground that the Examiner has applied an improper legal standard.

Since material incorporated by reference does not constitute new matter, the disclosure of the issued patent is deemed to include, as of its filing date, all such incorporated material. In particular, the disclosure of the issued patent is deemed to include, as of its original filing date, the actual text and figures of the incorporated H&L article explicitly added to the instant reissue application by amendment:

> Instead of repeating some information contained in anotherdocument, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. *The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.*

MPEP 2163.07(b) (emphasis added). *Any claim* that is supported by this disclosure in the manner prescribed by 35 U.S.C. §112, ¶1 likewise does not constitute new matter, and cannot be properly rejected as being based upon new matter under 35 U.S.C. § 251. *In re Rasmussen*, 211 USPQ 323, 326, footnote 6 (CCPA 1981); *Payet and Brummet v. Swidler and Wilson*, 207 USPQ 168, 170 (Bd. Pat. App.& Int. 1980). Thus, quite unlike the text and figures added explicitly into the instant reissue application by amendment, which correspond to the actual text and figures of the incorporated H&L article, *claims* based upon this incorporated material *need not appear verbatim* in the actual text of the incorporated reference or issued patent. They need only satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Accordingly, the question of whether Claims 7-73 stand properly rejected under 35 U.S.C. § 251 as being based upon new matter is answered by analyzing whether the disclosure of the issued patent, which *includes* the text and figures of the incorporated H&L article, supports Claims 7-73 in the manner prescribed by 35 U.S.C. § 112. If such support is found, then Claims 7-73 are not based upon new matter and cannot be properly rejected under 35 U.S.C. § 251.

Claims added to a reissue application satisfy the written description requirement of 35 U.S.C. § 112 if the disclosure of the issued patent, as originally filed, reasonably conveys to a skilled artisan that the inventor, at the time the issued patent application was filed, was in possession of the now-claimed subject matter. *Ralston Purina Co. v. Far-Mar-Co.*, 227 USPQ 177, 179 (Fed. Cir. 1985); *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983). The disclosure of the issued patent satisfies this standard for Claims 7-73, both as presently amended and as originally submitted.

As an initial matter, it is noted that the Examiner embeds within this new matter rejection a written description rejection under 35 U.S.C. §112, ¶1 (see Office Action at page 4, lines 3-11). Since the correct legal standard for assessing whether Claims 7-73 are based upon new matter is the same as that applied to determine whether Claims 7-73 are supported by the written description of the issued patent disclosure, all of the queries and allegations raised by the Examiner under the "New Matter" paragraph of the Office Action (numbered paragraph 8), are addressed together.

First, the Examiner alleges under both 35 U.S.C. § 251 and § 112, ¶1 that Claims 7-73 are directed to "method steps using 'double-flap' structures, hybridization complexes and kits" which are not supported by the disclosure of the issued patent. Applicant disagrees.

Regarding amended method Claims 7, 21 and 36, the original disclosure teaches diagnostic methods at Col. 11, lines 3-48 and again at Col. 42, line 63 through Col. 43, lines 36. The methods generally involve contacting a sample believed to contain a target nucleic acid (*see, e.g.,* Col. 42, lines 64-66) with a polynucleotide probe capable of specifically hybridizing to the target and forming, as a result of such hybridization, a 5'-flap structure that can be cleaved by a FEN-1 polypeptide (*see, e.g.,* Col. 42, line 67 through Col. 43, line 5). A specific embodiment of the methods is illustrated with reference to a particular species of such a 5'-flap structure, the 5'-single flap structure depicted in FIG. 6 (*see, e.g.*, Col. 43, lines 25-29). The original disclosure further teaches that the flap substrates and cleavage and binding reactions may be practiced with reference to several incorporated references, one of which is the incorporated H&L reference (*see, e.g.,* Col. 39, line 65 through Col. 40, line 3).

Additional 5'-single flap structures and another species of a 5'-flap structure, *a 5',3'-double flap structure*, are taught in the incorporated H&L article (*see, e.g.*, H&L article at page 4506, FIG. 5). This incorporated material expressly teaches that both 5'-single flap structures and 5',3'-double flap structures are bound and cleaved by a FEN-1 polypeptide (see *id.*).

Thus, the original disclosure teaches the recited methods, the recited cleavable 5',3'-double flap structures and that these structures possess the cleavage characteristics relevant for use in the methods.

Amended independent Claim 51 recites a hybridization complex comprising a bridge polynucleotide and two polynucleotide probes arranged in a 5',3'-double flap structure. This claim is fully supported by the various 5',3'-double flap structures described in the incorporated H&L reference (*see, e.g.*, H&L article at page 4506, FIG. 5).

Kits for carrying out the various described methods, as recited in amended independent Claim 59, are taught in the original patent at Col. 43, lines 38-52. The kits include a FEN-1 polypeptide having 5'-flap cleavage activity and may be used to practice the diagnostic assays according to the described methods (Col. 43, lines 39-42). From this, skilled artisans are taught that the kits may include additional reagents for carrying out the methods, such as polynucleotide probes that can hybridize with a target polynucleotide of interest to create a 5'-flap structure, for example the incorporated 5',3'-double flap structure, that is cleavable by the FEN-1 polypeptide. The original disclosure therefore supports amended independent Claim 59.

For the convenience of the Examiner, a table detailing where in the original patent disclosure each of Claims 7-73 finds written description support is provided below (in the table, "H&L" designates the incorporated H&L article):

Claim	Support: Col. (Lines)
7	11(3-41); 39(65)-40(18); 42(63)-43(36); H&L pp. 4506, Cols. 1 & 2; H&L FIG. 5
21	11(3-41); 39(65)-40(18); 42(63)-43(36); H&L pp. 4506, Cols. 1 & 2; H&L FIG. 5
36	39(65)-40(18); 40(19-34); H&L pp. 4506
8, 9, 34, 35	11(13-17); 43(5-12)
10-13, 26-30, 43-47, 69-73	FIGS. 1-5; 13(19-30)
14, 15, 31, 32, 48, 49, 56, 57, 62, 63	H&L FIG. 5; H&L pp. 4506, Col. 2, lines 3-20
16, 33, 50, 58, 64, 68	19(21-36); FIG. 6
17-19, 22-24, 40-42, 52-54, 60, 65-67	11(24-27); 43(20-22)
20, 25, 38, 55	11(27-28); 43(22-23)
37, 61	40(19-34)
39	H&L pp. 4504, Col. 2, lines 5-17 and 27-39
51	39(65)-40(3); H&L FIG. 5; H&L pp. 4506, Col. 2, lines 3-20
59	43(12-19); 42(63)-43(4); 43(39-53)

This table confirms that the original patent disclosure reasonably conveys to skilled artisans that the inventors were in possession of the inventions recited in Claims 7-73, both as presently amended and originally presented, at the time the original patent application was filed. The first paragraph of 35 U.S.C. § 112, first paragraph, demands no more.

Despite this detailed teaching, the Examiner contends, under the guise of 35 U.S.C. § 251, that there is no support in the original disclosure to indicate that the inventions of Claims 7-73 were conceived at the time the application was filed. However, as demonstrated above, the various methods, complexes and kits claimed find clear basis in the disclosure of the original patent.

It appears as though the Examiner's concerns may be directed to Claims 7-73 only to the extent they recite a double flap structure using certain specified language; *i.e.*, a double flap structure comprising a target nucleic acid comprising first and second portions. The allegedly objectionable language merely reflects one possible way of articulating the double flap structure that is very clearly described in the figures and text of the incorporated H&L article. For example, FIG. 5 of the incorporated H&L article teaches two specific cleavable double flap structures: one having a single nucleotide 3'-flap (below lanes 11-14; Double Flap #1) and another having a 10 nucleotide 3'-flap (below lanes 15-18; Double Flap #2). These double flap structures are also discussed in the text of the incorporated H&L article. Specifically, they are described as:

> a flap substrate that contained an Fadj strand that had either 1 nucleotide or 10 nucleotides of extra sequence at the 3'-end. Thus the base that contained the 3'- terminus was neither base-paired nor located in immediate juxtaposition to the elbow of the flap strand. This substrate, called a double flap structure, contained both a 5'- and a 3'- flap strand.

H&L article at page 4506, column 1, lines 8-14.

Such double flap structures or substrates are described in the present claims as a hybridized complex of:

1) a target nucleic acid comprising a first portion and a second portion located immediately 3' to the first portion,

2) a 5'-polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region that is capable of specifically hybridizing to the first portion of the target nucleic acid and a 5'-region located immediately 5' to the 3'-region; and

3) a 3'-polynucleotide probe comprising a 5'-region that is capable of specifically hybridizing to the second portion of the target nucleic acid and a 3'-region located immediately 3' to the 5'-region,

such that the 3'-region of the 5'-probe and the 5'-region of the 3'-probe specifically hybridize immediately contiguously with one another to the first and second portions, respectively, of the target nucleic acid molecule. For convenience, Applicant provides the following diagrammatic example of a double flap structure taken directly from FIG. 5 of the incorporated H&L article, and indicates the relation of each of its illustrated components to their description of a double flap structure in the present claims:

In the above figure, individual polynucleotide strands are illustrated as solid lines, with half-arrows at their 3'-ends. Strand **1** corresponds to a strand of the target nucleic acid. Clearly visible are the recited first and second portions which hybridize to specified regions of the 5'-polynucleotide probe (strand **2**) and the 3'-polynucleotide probe (strand **3**). These portions are also described in the text of the incorporated H&L article at page 4506, column 1, lines 8-14. Thus, the language of the claims merely articulates in writing the various features and arrangements of the polynucleotides comprising the exemplary double flap substrates depicted, and therefore described, illustratively in FIG. 5 of the incorporated H&L article.

The incorporated H&L article also teaches that this illustrated double flap structure can be specifically bound, and that the 5'-flap region of the 5'-polynucleotide probe **2** can be specifically cleaved, independent of polynucleotide sequence and 5'- or 3'-flap length. Accordingly, amended Claims 7-73, which recite various aspects of this (forming the double flap structure, binding and cleaving the double flap structure, using binding or cleavage of the double flap structure as an assay, kits comprising components for carrying out the various methods, etc.), are fully supported by the disclosure of the original patent.

The Examiner further alleges that Claims 14-16, 31-33, 48-50, 56-58 and 62-64, which recite double flap structures having 3'- or 5'-flap regions of specified lengths, are not supported. Again, Applicant disagrees. In the double flap structures of the incorporated H&L article discussed above, the 3'-polynucleotide probe has a flap region that is 1 nucleotide (Double Flap #1) or 10 nucleotides (Double Flap #2) in length. The 5'-flaps of both of these double flap structures are cleaved. From this, it is concluded that the 5'-flap cleavage requires only a 3' polynucleotide probe that forms a double stranded region adjacent to the 5'-flap, and that this 3' polynucleotide probe can optionally comprise a 3'-flap of variable length (see incorporated H&L article at page 4506, column 2, lines 3-20). The description of two exemplary double flap structures having 3'-flap regions that are 1 and 10 nucleotides in length, along with the disclosure that the 3'-flap region may be of variable length, is a description of a 3'-flap region that is from 1 to 10 nucleotides in length, as recited in Claims 14-15, 31-32, 48-49, 56-57 and 62-63.

Claims 16, 33, 50, 58 and 64, which specify that the 5'-probe has a 5'-flap region that is 1-20 nucleotides in length, are likewise supported by the disclosure of the original patent. The 5'-flaps of the cleavable substrates described in the original patent vary from 1 nucleotide, to 5 nucleotides (Col. 46, lines 46-58), to 20 nucleotides (incorporated H&L article at page 4506, FIG. 5, Double Flaps #1 and #2) in length. In addition, cleavage of the 5'-flap is taught as being" independent" of its length (Col. 19, lines 21-22). This disclosure provides ample support for Claims 16, 33, 50, 58 and 64.

In connection with the embedded rejection under 35 U.S.C. §112, ¶1, the Examiner also alleges that the claims lack a Flap endonuclease assay for measuring cleavage activity as well as hybridization conditions for use in complexes and kits. Applicant believes these rejections are duplicative of those raised in later sections. Accordingly, these rejections are addressed elsewhere in this Amendment.

Finally, the Examiner alleges that effective incorporation by reference is lacking. Yet, the Examiner previously acknowledged that the H&L article was properly incorporated (see Office Action, page 3, lines 6-9) . Indeed, in the sentence immediately following the allegation, the Examiner refers to this H&L article as being "properly incorporated" (see Office Action at page 4, lines 12-14). Since incorporation of the H&L article is expressly permitted by MPEP§ 2163.07(b), and the Examiner has acknowledged that the incorporation is proper, Applicant does not understand the basis for this objection. If this statement is intended to be a reiteration that the incorporated material is improper in that it allegedly does not fully support the present claims, Applicant disagrees for the reasons stated above.

Accordingly, for the reasons discussed above, Applicant submits that none of the subject matter added by amendment is "new" and that Claims 7-73, as presently amended and originally submitted, are fully supported by the disclosure as originally filed. Accordingly, the rejections of Claims 7-73 under 35 U.S.C. §§ 251 and 112 should be withdrawn.

4. REJECTION OF CLAIMS 7-10, 14-27, 31-44 and 48-70 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has rejected Claims 7-10, 14-27, 31-44 and 48-70 under 35 U.S.C. § 112, first paragraph, for lack of written description support. Applicant traverses the rejection.

Amended Claims 7-10, 14-27, 31-44 and 48-50 are drawn to methods comprising cleavage or binding of double flap structures which have a variety of uses, such as detection of target polynucleotides. The Examiner alleges that Applicant has failed to recite the structure of

the "claimed" endonuclease used for cleaving the double flap substrate. Note that Applicant is not claiming an endonuclease *per se*. Rather applicant is claiming *methods* of cleaving or binding a 5'-flap structure, and have provided methods for doing so in the disclosure. Applicant need not recite a particular structure for carrying out the steps of these methods. A method claim is a series of operational steps that may be carried out by any means; it is the series of operations that must be described, not the apparatus for carrying out each step of the method. Applicant has described the steps for carrying out each of the claimed methods, and need not recite a particular endonuclease used to perform the cleavage step.

Moreover, the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1 "Written Description" Requirement[1] ("Written Description Guidelines") indicate that the written description requirement for a claimed genus may be satisfied in several ways. One acceptable way is through the recitation of a number of representative species falling within the claimed genus. *See* Written Description Guidelines at page 1106, Col. 3, & (2); *The Regents*, 43 USPQ2d at 1406 ("A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus . . . .").

The instant application describes a representative number of species of endonucleases adequate to provide written description support for the genus. For example, the disclosure describes three species of FEN-1 polypeptides useful in the claimed methods: human FEN-1 (SEQ ID NO:1), murine FEN-1 (SEQ ID NO:3) and yeast FEN-1 (SEQ ID NO:5) (*see, e.g.*, Col. 13, lines 19-30). A fourth species which has the requisite endonuclease activity, but that differs in some other respects from the three species delineated above, is taught at Col. 54, lines 13-19 (ΔRAD2; SEQ ID NO:7). Further species of FEN-1 isolated from nuclear extracts of calf thymus, rabbit reticulocytes, Chinese hamster fibroblasts and Drosophila embryos are described at Col. 44, lines 23-27. These species adequately represent the genus of suitable endonucleases.

Moreover, amended Claims 7-10 and 14-20 describe the cleavage step functionally. Functional language has been approved consistently in claims drawn to combinations of elements. *See, e.g, In re Herschler*, 200 USPQ 711 (CCPA 1979); *In re Halleck*, 164 USPQ 647 (CCPA 1970); *In re Fuetterer*, 138 USPQ 217 (CCPA 1963); *In re Boller*, 141 USPQ 740 (CCPA 1964). For example, in *In re Fuetterer*, a functional description of a genus of salts was held proper in a claim to a composition comprising the salts and other ingredients. *In re*

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[1] Federal Register 66(4):1099-111 (January 5, 2001).

Fuetterer, 138 USPQ at 222 ("inorganic salt that is capable of holding a mixture of said protein and/or carbohydrate in colloidal suspension" upheld in claim to a rubber stock for producing tire treads). In *In re Herschler*, a functional description of a genus of steroids was held proper in a claimed method of enhancing the penetration of a physiologically active steroidal agent across an external barrier membrane of a human or animal subject using an effective amount of DMSO.

Accordingly, Applicant submits amended Claims 7-10, 14-20, 21-27, 31-44 and 48-70 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection as it applies to these claims is therefore requested.

5. REJECTION OF CLAIMS 7-73 FOR LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7-73 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. Applicant traverses the rejection.

To support the rejection, the Examiner suggests that the recitation of probes that hybridize to target polynucleotides requires that Applicant define the conditions under which the hybridization takes place. According to the Examiner, without a clear and explicit recitation of the conditions which were actually used by Applicant in "isolating the claimed polynucleotides which hybridize to the disclosed sequences", the skilled artisan would not be able to practice the claimed invention and would not be reasonably apprised of the metes and bounds of the claimed invention.

It appears that the Examiner has misunderstood the inventions of amended Claims 7-73. Applicant is not claiming nucleic acids by their ability to hybridize to disclosed polynucleotide sequences. In particular, this is *not* a situation where the novelty of a particular *claimed* nucleic acid is defined by its ability to hybridize to a specifically disclosed sequence under specified conditions. Rather, amended Claims 7-50 recite methods that utilize polynucleotides that can adopt a specific structure, a 3',5'-double flap structure, that can be specifically bound and cleaved by a FEN-1 polypeptide. Amended Claims 59-73 recite kits for carrying out the methods. As clearly taught throughout the disclosure, the cleavage is dependent only upon the presence of the double flap structure, and *is independent of the particular sequences of the polynucleotides forming the structure*. Even amended Claims 51-58, which are drawn to the 5',3'-double flap hybridization complex *per se,* recite the complex by virtue of its ability to adopt or form the requisite structure which, as discussed above, does not depend on the specific

sequences of the recited polynucleotides beyond requiring that they have sequences which are capable of forming the structure. As a consequence, Applicant need only enable the double flap structure, and need not provide every sequence of every set of target polynucleotide, 3'-probe and 5'-probe, and the hybridization conditions therefor. Having described the double flap structure, Applicant has enabled the skilled artisan to readily determine the sequences of the 3'- and 5'-probes and the hybridization conditions necessary to form a double flap structure given any particular target sequence.

In addition, the Examiner has overlooked a very important fact: Applicant has taught hybridization conditions that actually work. For example, the incorporated H&L article teaches hybridization conditions under which 5'-flap cleavage was detected. As formation of a hybridization complex is necessary for such cleavage, the conditions described for these experiments are examples of the many that are suitable for formation of a double flap hybridization complex. Suitable conditions for practicing the claimed methods, hybridization complexes and kits are also taught, for example, at Col. 39, line 65 through Col. 40, line 18. Additional conditions are taught in the various articles incorporated by reference at Col. 39, line 65 through Col. 40, line 3. For example, as evidenced in the respective articles, the binding and cleavage reaction conditions incorporated from Harrington & Leiber, 1994, *EMBO J.* 13(5):1235-46 and Harrington & Lieber, 1994, *Gene & Development* 8(11):1344-55 articles are suitable for practicing the claimed inventions. Additional conditions for carrying out hybridizations and cleavage are taught in the working examples at, for example, Col. 49, line 51 through Col. 52.

Moreover, as explicitly taught in the original disclosure, the actual conditions are not critical for success, and various modifications may be made. *See, e.g.*, Col. 40, lines 9-18. Guidelines for determining which modifications are suitable are provided at Col. 40, lines 13-18.

Accordingly, from the teachings in Applicant's disclosure, combined with the knowledge available in the art, ordinarily skilled practitioners would have had no difficulty in making operative the inventions as claimed. As a consequence, the enablement requirement is satisfied and the rejection should be withdrawn.

6. REJECTION OF CLAIM 7 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 7 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting essential elements. The Examiner alleges that cleavage, release, incubation, detection and quantification steps are missing. The rejection is traversed. Regarding

the detection and quantification steps, Applicant notes that amended Claim 7 recites detecting and/or quantifying the cleavage. As noted in the original patent at Col. 11, lines 11-17, cleavage can be detected and optionally quantified. Accordingly, both steps are not required and it is proper to recite "detecting" and "quantifying" in both the alternative and in combination.

Applicant submits no other steps have been omitted. Step (b) of Claim 7 recites "selectively cleaving" the polynucleotide to release a nucleotide or a polynucleotide from its 5'-region. This step subsumes the cleavage, release and incubation steps the Examiner believes are omitted. While the disclosure at Col. 11, line 11 recites "incubating with FEN-1," when read in the context of the complete disclosure, skilled artisans are taught that this passage supports step (b) as presently drafted. Specifically, the definition of FEN-1 makes it clear that this expression is generic in scope. The entire disclosure teaches that FEN-1 is an endonuclease capable of specifically cleaving certain polynucleotides. Applicant reminds the Examiner that the claimed subject matter need not be described *in haec verba* to satisfy the written description requirement. *In re Herschler*, 200 USPQ 711, 717 (CCPA 1979). The disclosure need describe the claim limitations only so clearly that one having ordinary skill in the art would recognize that the inventors invented the method including the claimed limitations. *Id.* This requirement has been met.

Accordingly, Applicants submit no essential elements of amended Claim 7 are omitted, and that amended Claim 7 satisfies the second paragraph of Section 112. Applicants therefore request that the rejection be withdrawn.

7. REJECTION OF CLAIMS 7-73 UNDER 35 U.S.C. § 103(a)

Claims 7-73 stand rejected under 35 U.S.C. § 103(a) as being obvious over Harrington & Lieber, 1994, *EMBO Journal* 13(5):1235-1246 ("Harrington & Lieber II"). Applicant traverses the rejection on the ground that the Examiner has failed to establish a *prima facie* case of obviousness.

When rejecting claims under 35 U.S.C. § 103(a), the Examiner bears the burden of establishing a *prima facie* conclusion of obviousness. In order to do so, the Patent must demonstrate three elements: (1) that the prior art provides a suggestion or motivation to modify or combine the teachings of the references relied upon by the Office to reject the claims; (2) that the prior art provides one of skill in the art with a reasonable expectation that the suggested combination or modification would be successful; and (3) that the prior art, either alone or in combination, teaches each and every limitation of the rejected claims. The teaching or

suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). See also, *WMS Gaming Inc. v. Int'l. Game Technology*, 51 USPQ2d 1385, (Fed. Cir. 1999). These three elements are distinct. If any one is not established, *prima facie* obviousness is not established, and Applicant is *not* required to show indicia of unobviousness, such as new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

The cited Harrington & Lieber II article fails to render amended Claims 7-73 *prima facie* obvious. In particular, the Harrington & Lieber II article does not teach or suggest double-flap structures. Each of independent amended Claims 7, 21 and 36 recites a method involving cleavage of a double-flap structure. Likewise, amended independent Claim 51 recites a hybridization complex having a double-flap structure and amended independent Claim 59 recites a kit for detecting the presence of a target nucleic acid comprising, *inter alia*, probes capable of hybridizing with the target so as to form a double-flap structure. All of the remaining claims ultimately depend from these independent claims.

The Examiner points out that the phrase "double flap" is not expressly recited in the claims. Applicant need not use this term, but instead need only establish that the substrate of the present claims does not include the bifurcated structure taught in Harrington & Lieber II. The bifurcated structure taught in Harrington & Lieber II is depicted in Figure 1, page 1236 and is described in the Abstract, page 1235. Figure 1 clearly shows a single 5'-flap. The substrate of the present claims, as is established above by reference to FIG. 5 of the incorporated H&L article, comprises a 3'-flap in addition to a 5'-flap. The bifurcated structure is described in the abstract as "composed of double-stranded DNA and a displaced single-strand." No structure disclosed in Harrington & Lieber II has more than a single flap. Since the cited Harrington & Lieber II article fails to teach or suggest the structure of the hybridization complex recited in the present claims, or to provide any reasonable expectation that such structures could be cleaved, it does not render amended Claims 7-73 obvious. Accordingly, Applicant requests that the rejection of Claims 7-73 under 35 U.S.C. § 103(a) be withdrawn.

8. CONCLUSION

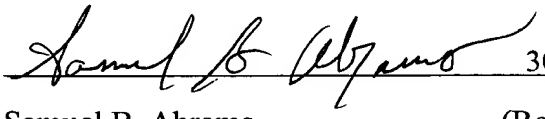
For the reasons discussed above, Claims 7-73 satisfy all requirements for patentability and are in condition for allowance. An early notification of the same is therefore kindly requested.

If the Examiner determines that prosecution of the instant application would benefit from a telephonic interview, the Examiner is invited to call the undersigned attorney.

No fees are believed due in connection with this response. However, the Examiner is authorized to change any deficient or required fees, or to credit any over payment, to Pennie & Edmonds, LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date March 10, 2003



30,605

Samuel B. Abrams (Reg. No.)

Enclosures

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EXHIBIT A

Marked-Up Copy of Amended Claims

7. (Twice Amended) A method of cleaving a polynucleotide, comprising the steps of:

(a) contacting a sample suspected of containing a target nucleic acid of interest, said target nucleic acid comprising a first portion and a second portion located immediately 3' to the first portion, with:

(i) a 5'-polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region that is capable of specifically hybridizing to the first portion of the target nucleic acid and a 5'-region located immediately 5' to the 3'-region; and

(ii) a 3'-polynucleotide probe comprising a 5'-region that is capable of specifically hybridizing to the second portion of the target nucleic acid and a 3'-region located immediately 3' to the 5'-region,

under conditions in which the 3'-region of the 5'-probe and the 5'-region of the 3'-probe specifically hybridize immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule;

(b) selectively cleaving the 5'-polynucleotide probe to release a nucleotide or a polynucleotide from its 5'-region; and

(c) detecting [or] and/or quantifying said cleavage.

21. (Amended) A method of detecting the presence of a target nucleic acid in a sample, comprising the steps of

(a) contacting a sample suspected of containing a target nucleic acid of interest with:

(i) a FEN-1 polypeptide;

(ii) a 5'-polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region that is capable of specifically hybridizing to a first portion of the target nucleic acid and a 5'-region located immediately 5' to the 3'-region; and

(iii) a 3'-polynucleotide probe comprising a 5'-region that is capable of specifically hybridizing to a second portion of the target nucleic acid which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region,

under conditions in which the 3'-region of the 5'-probe and the 5'-region of the 3'-probe specifically hybridize immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule; and

(b) detecting the presence or absence of, [or] and/or quantifying the amount of, FEN-1 polypeptide-generated cleavage, thereby detecting the presence of the target nucleic acid in the sample.

36. (Amended) A method of detecting the presence of a target nucleic acid in a sample, comprising the steps of:

(a) contacting a sample suspected of containing a target nucleic acid of interest with:

(i) a FEN-1 polypeptide;

(ii) a 5'-polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region that is capable of specifically hybridizing to a first portion of the target nucleic acid and a 5'-region located immediately 5' to the 3'-region; and

(iii) a 3'-polynucleotide probe comprising a 5'-region that is capable of specifically hybridizing to a second portion of the target nucleic acid which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region, under conditions in which the 3'-region of the 5'-probe and the 5'-region of the 3'-probe specifically hybridize immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule to form a structure that the FEN-1 polypeptide is capable of binding, thereby yielding a target-FEN-1 complex; and

(b) detecting the presence or absence of the target-FEN-1 complex, thereby detecting the presence of the target nucleic acid in the sample.

51. (Twice Amended) A hybridization complex comprising:

(a) a bridge polynucleotide comprising a first portion and second portion located immediately 3' to the first portion;

(b) a first polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region and a 5'-region located immediately 5' to the 3'-region; and

(c) a second polynucleotide probe comprising a 5'-region and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the first probe and the 5'-region of the second probe are specifically hybridized immediately contiguously with one another to the first and second portions, respectively, of the same bridge polynucleotide molecule, thereby forming a hybridization complex.

59. (Twice Amended) A kit for detecting the presence of a target nucleic acid in a sample, comprising:

(a) a FEN-1 polypeptide;

(b) a first polynucleotide probe capable of being cleaved by a FEN-1 polypeptide, comprising a 3'-region capable of specifically hybridizing to a first portion of a target nucleic acid of interest and a 5'-region located immediately 5' to the 3'-region;

(c) a second polynucleotide probe comprising a 5'-region capable of specifically hybridizing to a second portion of the target nucleic acid which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the first probe and the 5'-region of the second probe are capable of specifically hybridizing immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule to form a structure that is capable of being bound or cleaved by the FEN-1 polypeptide.

EXHIBIT C

BOX: MISSING PARTS

Express Mail No. EL 451 595 066 US ~~First Class Mail (xx)~~
Date Mailed September 11, 2000
Ser. No. 09/586,744 Filed 6/2/00
Inventor Harrington et al.
For MAMMALIAN FLAP-SPECIFIC ENDONUCLEASE

(✓) Response to Notice of Missing Parts of Application-Filing Date Granted (+Copy)

( ) Affidavit/Declaration
( ) Amendment
( ) Application ____ Pages
( ) ____ Claims ____ Drawings
( ) Appeal, Notice of
( ) Assignment
( ) Brief (in triplicate)
( ) Declaration & Power of Attorney
( ) Design Application
( ) Disclaimer
( ) Disclosure Statement
( ) w/refs. ( ) w/o refs.
( ) Drawings Formal
____Sheets ____Figures
( ) Fee Address Indication Form
( ) Fee Calculation
( ) Issue Fee Transmittal
( ) Letter
( ) Oral Hearing Req./Confirm.
( ) Petition to Extend Time
( ) Pet. under 37 C.F.R.
( ) Power of Attorney
____Associate____w/Revocation
( ) Sequence Listing w/Computer Readable and Paper Copies
( ) Small Entity Statement
( ) Status Letter
( ) Transmittal Letter

OIPE SEP 11 2000 PATENT & TRADEMARK OFFICE

(✓) Certification Under 37 CFR §3.73(b) and Revocation and Power of Attorney
Other: Consent of Assignee; Offer to Surrender Patent; Reissue Application Declaration by the Inventors (2); Copy of Notice to File Missing Parts...
File No. 9584-0017-999 Sender: SBA/AMP/rac

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Reissue Application of: Harrington *et al.*

Serial No.: 09/586,744 | Group Art Unit: not assigned

Filed: June 2, 2000 | Examiner: not assigned

For: MAMMALIAN FLAP-SPECIFIC ENDONUCLEASE | Attorney Docket No.: 9584-017-999

OFFER TO SURRENDER PATENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The captioned application is a reissue application of U.S. Patent No. 5,874,283, entitled "MAMMALIAN FLAP-SPECIFIC ENDONUCLEASE," which issued on February 23, 1999 to Harrington *et al.* PE Corporation is the assignee of the entire interest in U.S. Patent No. 5,874,283 and offers to surrender the original patent.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee. A certificate under 37 CFR § 3.73(b) is being filed concurrently herewith.

I hereby declare that all statements made herein of my own knowledge are true, and that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United states Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully Submitted,
PE Corporation

Dated: August 18, 2000

By: _____
Name: Joseph H. Smith
Title: Vice President